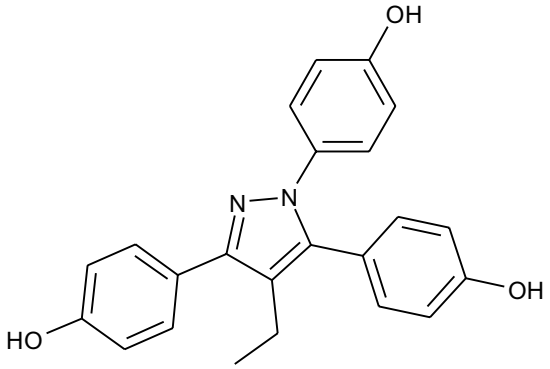
Highlights from other journals – January 2001

Estrogen receptor ligands

Novel estrogens having tissue selective action suitable for menopausal hormone replacement or the treatment and prevention of breast cancer are current targets of interest. A solid phase parallel approach has been used to discover small molecule estrogen receptor ligands (Solid-phase synthesis of tetrasubstituted pyrazoles, novel ligands for the estrogen receptor, S. R. Stauffer and J. A. Katzenellenbogen, *J. Comb. Chem*., 2, (2000), 318-329). A library of 96 individual compounds was synthesised on Merrifield solid phase resin. Synthesis incorporated a crossed-Claisen condensation, forming a resin bound β-diketone, followed by treatment with a substituted hydrazine derivative to form the resin bound tetrasubstituted pyrazole. Subsequent acid cleavage delivered these compounds ready for biological testing. Several series were identified which displayed a relative binding efficiency (RBA) of greater than 13% compared to estradiol, which has an RBA of 100% against the estrogen receptor. One of the most potent compounds prepared from this library (i) possessed an RBA against the estrogen receptor of 23%. From this approach, several interesting binding patterns have emerged and this work provides a direction for further exploration of tetrasubstituted pyrazoles in the search for highly potent agonists, or antagonists against the estrogen receptor.



(i)

Amino acid-DNA contacts

Basic helix-loop-helix (bHLH) transcription factors are characterised by a conserved, parallel four-helix bundle that recognises a specific hexanucleotide DNA sequence in the major groove. The least characterised region of these proteins is the loop region, ranging in size from 5 to 23 amino acids with the loop varying in amino acid content, especially between proteins of different subfamilies. Loop regions may play more than a structural role, by contributing to DNA-binding affinity and/or specificity through phosphate-backbone or base-specific interactions. Protein-DNA recognition by the *Drosophila* bHLH transcription factor Deadpan was probed using combinatorial solid-phase peptide synthesis (Rapid identification of key amino-acid-DNA contacts through combinatorial peptide synthesis, R. L. Winston and J. M. Gottesfeld, *Chemistry & Biology*, 7, (2000), 245-251). A depsipeptide unit (a peptide that contains an amide to ester substitution) was scanned through the loop region corresponding to the bHLH domain of the *Drosophila* transcription factor Deadpan. A series of bHLH peptide libraries that modulate amino acid content and length in the amino-terminal or carboxy-terminal region of the loop was screened with DNA and peptide affinity columns. From this work, a functional bHLH peptide with reduced loop length was found and Lys80 was

unambiguously identified as the sole loop residue critical for DNA binding. This method therefore provides a rapid alternative to standard recombinant techniques for the generation and assay of mutant proteins. The ability to replace key residues involved in protein-protein or protein-DNA recognition, especially with unnatural amino acids or other such small molecules, provides a powerful tool to probe energetic contributions to molecular recognition and hence new drug design.